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A1)  
THE PROCESS FOR MANUFACTURING FORMULATION OF TOPICAL  
BETA BLOCKERS WITH IMPROVED EFFICACY.

The present invention relates to a process of manufacturing a formulation of Beta-blockers with improved efficacy and tolerance. Beta-blockers are used as topical ophthalmic preparations for reducing intraocular pressure.

The present invention is directed to manufacturing of a formulation containing Beta-blockers in such a way so that pressure lowering effects of Beta-blockers are improved. Beta-blockers are required to be used for a long time for reduction in I.O.P. Their prolonged use is associated with instability of tear film leading to dry eye. The present invention is also directed to manufacturing of a formulation containing Beta-blockers in such a way so that tear film is stabilized.

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A2)  
Beta-blockers are known to reduce I.O.P. mainly by reduction in aqueous secretion. This reduction in aqueous secretion is dose dependent. However, increasing the dosage beyond a point does not improve its capacity to reduce I.O.P. For timolol, levobunolol and Betaxolol it is achieved at 0.5% concentration for carteolol it is 1% and for metipranalol it is 0.3%. Increasing concentration beyond this does not result in further reduction in I.O.P.

The attempts made to improve its efficacy are not successful. In clinical situation when further reduction in I.O.P. is desired another drug like, Pilocarpine, Dipivefrin hydrochloride, Dorzdamide, Brimonidine, Latanoprost, etc. is added to it.

The formulations of Beta-blockers used are usually aqueous in nature.

There are sustained release preparations available for Beta-blockers. The formulation of pilocarpine in sustained release preparation is required to be doubled i.e. for I.O.P. reduction as much as 2% pilocarpine solution, 4% pilocarpine gel is required. Betaxolol is available as Betoptic-s and of timolol is Timoptic-XE. In both formulations vehicle used are different. With this it is possible to reduce concentration of Betaxolol used, but it is not possible to improve effect on I.O.P. Similarly, it is possible to reduce frequency of administration from twice a day to once a day with timoptic-XE. However, pressure lowering effect remains same. The formulations made with hydroxyl propyl methyl cellulose are found to be of no advantage compared to aqueous formulation.

Similarly, sustained release preparation of pilocarpine (Pilopine-HS gel) is also available. It contains Carbopol as a vehicle. The duration of action is prolonged but pressure reducing effect is reduced. To get the pressure lowering effect as much as aqueous solution, concentration of pilocarpine in sustained release preparation is required to be doubled i.e. for I.O.P. reduction as much as 2% pilocarpine solution, 4% pilocarpine gel is required.

The objective of present invention is to provide formulation of Beta-blockers with improved efficacy.

The further objective of present invention is to provide formulation of Beta-blocker which stabilizes the tear film.

The further objective of present invention is to provide a formulation of Beta-blockers which is effective after longer period of storage.

The further objective of present invention is to minimize/eliminate Beta-blocker entering systemic circulation.

The further objective of present invention is to increase compliance by reduction/elimination of side effects of Beta-blockers.

The further objective of present invention is to provide formulation in a concentration which is known to provide maximum I.O.P. lowering effect in a conventional aqueous formulation.

Accordingly, there is provided a process of manufacturing formulation of topical beta blocker with improved efficacy which comprises of the following steps :

1. The aqueous solution of Beta-blocker is made which contains acceptable excipients, buffers and preservative in distilled water. The pH of this solution is adjusted to 7.0 to 7.5.

2. In a separate vessel Carbopol is dissolved into water and stirred well till gel is formed. Preservatives and buffers are added to it gradually while stirring. The pH of solution is adjusted to pH 6.5 to 7.5.
3. Solution containing Beta-blocker as formulated in step 1 is gradually added to the gel as formed in step 2.
4. Volume is made up by adding distilled water as required.
5. pH is checked and adjusted as necessary to keep it in range of  $7.0 \pm 0.5$ .

Beta-blockers described above can be timolol 0.5%, Betaxolol 0.5%, Levobunolol 0.5%, Carteolol 1.0%, metipranolol 0.3% or any other Beta-blocker which can reduce I.O.P in a therapeutic concentration.

Carbopol can be carbopol 940, 932 970 or others which forms gel in aqueous solution. The concentration of carbopol in final formulation can be from 0.5% to 5%.

The buffer which can be used, can be any, used in topical ophthalmic preparation e.g. dibasic sodium phosphate sodium phosphate mono basic etc.

The preservative can be EDTA, Benzyloconium chloride, Cetrimide or any other which can be used in ophthalmic topical preparation in a dosage recommended.

pH is usually acidic and needs to be adjusted by sodium hydroxide.

The final product is autoclaved and put into a sterile packaging.

## Example of formulation

## I. Timolol 0.5%

Timolol maleate	0.72 gm equivalent to 0.5 gm of timolol
Benzylconium chloride	0.0107 gm
Carbopol 940	2.0 gm
Sodium hydroxide to adjust pH	6.5 to 7.5
Water for injection	QS to make 100 ml.

## II. Betaxolol 0.5%

Betaxolol hydrochloride	0.56 gm equivalent to 0.5 gm of Betaxolol
Benzylconium chloride	0.01 gm
Di basic sodium phosphate	0.05 gm
Sodium phosphate mono basic	0.025 gm
Di sodium EDTA	0.05 gm
Sodium chloride	0.30 gm
Propylene glycol	2.50 gm
Carbopol 940	2.00 gm
Water for injection	QS to make 100 ml of solution

The pharmaceutical composition so manufactured is evaluated for stability and efficacy.

The pharmaceutical composition so manufactured is evaluated at different test conditions of temperature and humidity (45° C, 37° C at 80% relative humidity and ambient temperature), for time interval extending upto 12 months.

The samples of formulation were taken for study.

The formulation of timolol 0.5% made as described (new formulation) was evaluated in healthy volunteers as well as in eyes having raised intraocular pressure.

In a single dose paralleled study timolol 0.5% eye drops (conventional formulation) were instilled in one eye and new formulation was instilled in the other eye of 11 patients. Timolol eye drops caused drop in I.O.P. by 23.49% while new formulation caused drop in I.O.P. by 38.7%.

In a single dose cross over study (10 eyes) new formulation as well as conventional formulation (eye drops) were instilled in same eye on different days, but at the same time of day. It was found that reduction in I.O.P. with conventional formulation was 22.36% while that with new formulations was 37.7%.

Thus improved efficacy of new formulation is established in healthy volunteers.

Similarly, in glaucomatous eyes (14), both formulations (conventional and new) were evaluated. Even in glaucomatous eyes the reduction in I.O.P. noticed was much more than that seen with conventional formulation. With conventional formulation it was 33.35% while with new formulation drop in I.O.P. was 44.4%.

The effect on reduction in I.O.P. seen in glaucomatous eyes was further evaluated by long term application in 14 eyes. It was found that effect is maintained even on long term application. The drop in I.O.P. in glaucomatous eyes was 44.4% at 15 days, 43.6% at one month and 43.6% at three months interval.

Thus new formulation was found to have improved efficacy in glaucomatous eyes. This improved efficacy was found to persist even on long terms application.

Like eye drops of timolol, increasing concentration of timolol in new formulation from 0.5% to 1.0%, further drop in I.O.P. was not seen. However, this resulted in increase in duration of its action.

When other antiglaucoma drugs were added to therapy in persons using new formulation it was found to reduce I.O.P. further. This further reduction in I.O.P. was as good as seen with combination of antiglaucoma drugs with timolol eye drops.

Similarly, when formulation with other Beta-blockers like, Betaxolol were made as per process described in this invention it was also found to cause further drop in I.O.P. compared to conventional formulation.

Traditionally made viscous formulation for use as topical ophthalmic preparations are known to cause disturbances in vision. However, none of the person in whom new formulation were used complained of visual disturbances 5 minutes after instillation of new formulation.

1. A process of manufacturing of formulation of topical beta blockers with improved efficacy comprising the following steps :

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- i) a. Making aqueous solution of Beta-blocker with or without physiologically acceptable excipients, buffers and preservatives.
  - b. Making a gel of known gel forming substance with or without physiologically excipients buffers and preservatives in a separate vessel.
  - ii) Adding aqueous solution of Beta-blockers at step i(a) into a prepared gel of step i(b) while stirring slowly.
  - iii) Adjusting the pH and volume before finally autoclaving and packaging.

2. A process as claimed in claim 1 wherein Beta-blockers can be selected from topical Beta-blockers used to reduce intraocular pressure, e.g. Timolol, Betaxolol, Carteolol, Metipranolol.

3. A process as claimed in claim 1 & 2 wherein gel forming agent can be carbopol.

4. A process as in claim 1 to 3 wherein concentration of carbopol can be from 0.5% to 5%.

5. A process as claimed in claim 1 to 4 in which physiologically acceptable buffers, excipients and preservatives are used.

6. A process as claimed in claim 1 to 5 wherein pH of formulation is finally adjusted to between 6.0 to 8.0 preferably between 6.5 and 7.5.

7. A process as claimed in claim 1 to 6 wherein formulation is autoclaved before packaging.

8. A process as claimed in claim 1 and substantially herein described in example I & II in the accompanying specification.